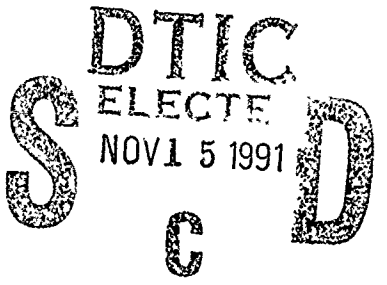

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Department of the Navy

Naval Medical Research and Development Command

Combat Casuaity Care Research

Naval Medical Center

Bethesda, Maryland 20814-5044

Status report covers progress made through the period

June 1, 1991 through September 30, 1991

on N00014-89-J-3124

P.I. Harvey I Miller, Ph.D.

Metabolic Changes and Hemodynamic Dysfunction Following Hypothermic Shock

Grant Number: N00014-89-J-3124

Harvey I Miller, Ph.D. - Principal Investigator

STATUS REPORT

From June 1, 1990 To September 31, 1991

Sudden chilling of the entire body by immersion in a very cold water environment, overwhelms the temperature regulatory system and the core temperature starts falling rapidly. When the core temperature falls below 35°C, the individual is considered to be hypothermic. There are two classes of hypothermia, iatrogenic and accidental. The iatrogenic type refers to lowering the body temperature to aid surgical or chemical therapy in cardiac, neurologic or neoplastic diseases. Accidental hypothermia is a nonpurposeful lowering of the body temperature due to untoward circumstances which place the individual in a situation in which the ambient temperature is so low that the normal temperature regulatory mechanisms of the body can not work. Accidental hypothermia can be further divided into 3 levels: mild (temperature between 35°C and 32°C) moderate (temperature between 32°C and 28°C) and severe (temperature below 28°C). Because of the nature of the military's mission, the possibility of becoming severely hypothermic is common. The usual treatment is to warm the body by external heat (electric blankets, covers, warm water etc.), peritoneal lavage and cardiovascular bypass. There is apparently no difference between the various rewarm procedures as to recovery and survival. However, many individuals survive the initial insult only to

succumb 2 or 3 days later to cardiogenic shock. This led us to the hypothesis that: "Acute severe accidental hypothermia produces long term perturbations which may produce permanent injury or death."

We have shown that following immersion hypothermia and rewarming a cardiac dysfunction was observed that persisted for at least 48 hours. Cardiovascular compensatory mechanisms overshadowed the dysfunction and it was not readily apparent in the whole animal. However, if hearts from hypothermic animals are isolated from neural and endocrine influences by using the perfused working heart preparation, they exhibit depressed Starling curves. In other words, hearts from these hypothermically shocked animals have decreased physiologic reserve. If the animal's physiologic reserve is low to begin with, then the animal may not survive. The guinea pigs we use are Duncan-Harley stain. They have an absolute requirement for Vitamin C. However, they appear to do better if the source of the ascorbic acid is from greens. In fact, it is our impression that survival of the model increases if they are fed cabbage or some other leafy vegetable. Due to some mixup in or animal facility, our guinea pigs did not receive any greens for a month, survival decreased. We believe physiologic reserve decreased.

Progress was made in measuring plasma catecholamines in the cool-down and rewarm phase of hypothermia.

Guinea pigs, who were fed leafy greens for at least 2 weeks prior to the experiment, had indwelling catheters and a thermistor emplaced as described in earlier progress reports. On the day of the experiment, they were temporarily anesthetized with a short acting barbiturate, Brevital®, and immersed neck-deep in ice-water until their core temperature fell to 25.5°C. This process took from 6-7 minutes. Observations were

recorded and blood samples taken at 30 seconds and then each minute. The animal was then wrapped in a heating pad and warmed until the core temperature returned to 38.5°C. Even though the guinea pig was being warmed, during the first few minutes the temperature continued to fall. When it reached its lowest point (LBT), blood samples were withdrawn and recordings of heart rate, blood pressure and body temperature were obtained. Then body temperature began to rise slowly. When it reached 38.5°C, some 45 minutes later blood samples were withdrawn and recordings were again obtained. This point was considered 0 time. Recordings and blood samples were also taken at 1, 2, 3, 4 and 24 hours.

Figure 1 shows the changes in body temperature from control samples, through the cool down, rewarm and 1, 2, 3, 4 and 24 hours after return to normal temperature, as well as a blowup of the interval between the control and lowest body temperature (LBT). At 30 seconds the body temperature does not fall perceptively. Even at 1 minute post immersion there is only a small drop. At 2 minutes, there is a significant drop which continues to the LBT. The control animal, immersed in warm (38-39°C) water has a body temperature decrease of only a few degrees which is restored with a few minutes exposure to the heating pad.

During cool-down, plasma norepinephrine concentration (NorEpi) steadily rose (Figure 2). At 6 minutes post immersion, when the body temperature reached 25.5°C, Norepi levels rose to 2 x that of control. In some very preliminary data the Norepi levels are elevated 10-fold at 4 and 24 hours post rewarm. Epinephrine changed variably. With the high norepinephrine levels one would expect the free fatty acids, FFA, to be elevated but we have not observed that (Figure 3). While the blood glucose levels of both the hypothermic and control animals rise during cool down, they return to normal values at

0 time in the controls and fall to low levels at 2 hours post return to normal temperature reflecting insulin release (Figure 4). By 4 hours they are essentially normal. The hypothermic animals peak at 0 time. However, by 4 hours they are normal. Lactate rises steadily in the hypothermic and controls, but the elevation of control lactate levels, while statistically significant are slight, while the hypothermics are large, reflecting ischemia in the peripheral tissues with wash out or rewarm (Figure 5). The arterial pH shows that the hypothermics have a metabolic acidosis that persists more than 4 hours (Figure 6).

These metabolic studies suggest that while there are very large increases in circulating catecholamines, the catecholamines are less sensitive in the hypothermics post rewarm. Heart rate is elevated almost immediately upon immersion in cold water and does not fall until 2 minutes after immersion. When the body temperature returns to normal (0 time) so does the heart rate (Figure 7); even in the face of high catecholamine levels. It would appear that the adrenergic receptors are downregulated and appear less sensitive.

This may be the reason for lack of elevation of the FFA. However, there may be another explanation. The "Adipose Tissue Electric Blanket Theory" suggests 2 roles to the subcutaneous adipose tissue. 1) It is a very good insulator and preserves the heat in the core. 2) The cycling of triglyceride, the major component in adipose tissue, is hydrolyzed to 3 FFA and glycerol and then reesterified into triglyceride. The product of this cycle is heat. Hormone sensitive lipase controls this cycle (Figure 8). Norepinephrine controls hormone sensitive lipase activity. The reason for the lack of elevation of plasma FFA might be an increase in the internal cycling of fatty acids to produce more heat. However, the hypothermic animals' adrenergic receptors appear to be downregulated and these animals have a difficult time maintaining core temperature even 4 hours after

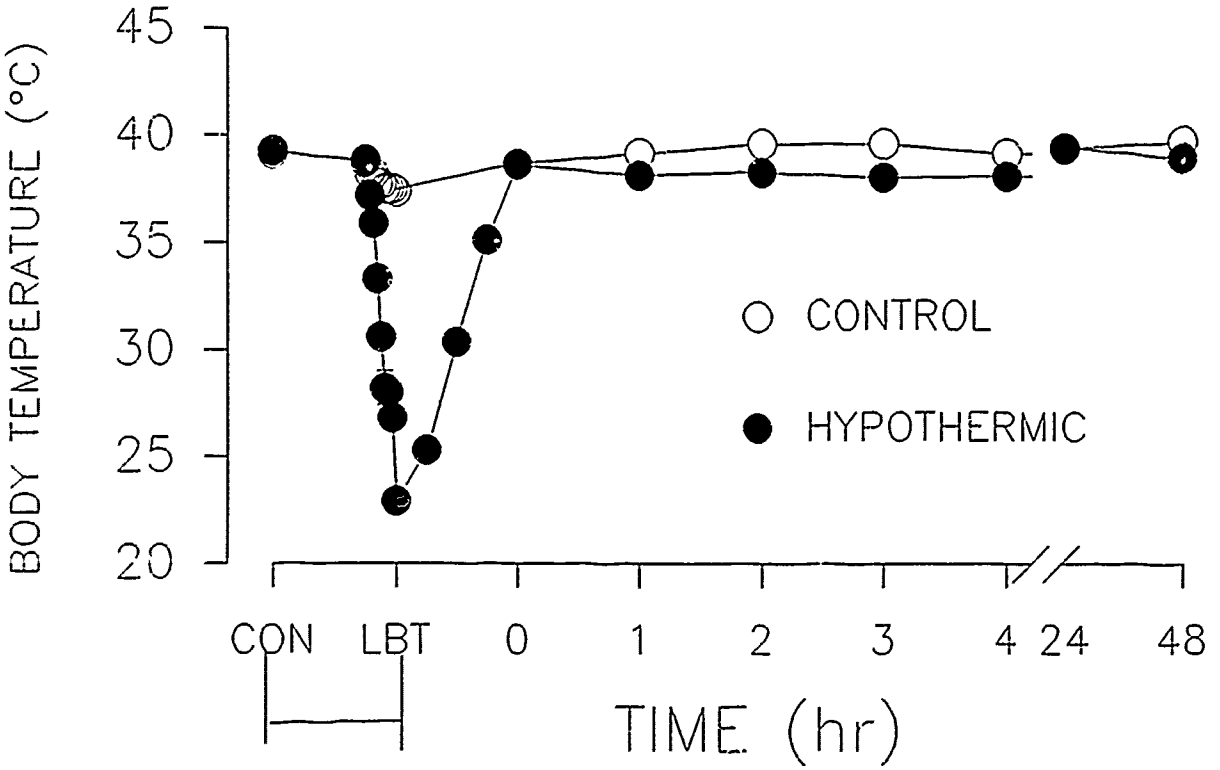
rewarm. It is more than likely that the hormone sensitive lipase is depressed, the futile cycle is slowed, and heat production within the adipose tissue is depressed.

In order to study these phenomena we are measuring both plasma FFA and glycerol to determine the retention of FFA by adipose tissue. Since the freed glycerol cannot be rephosphoralated within the adipose tissue, glycolysis must supply the α glycerophosphate, so that the ratio of glycerol to FFA in the plasma is a reflection of adipose tissue reesterification. In this way we can tell whether the loss of temperature regulatory ability is due to a short circuit of the electric blanket.

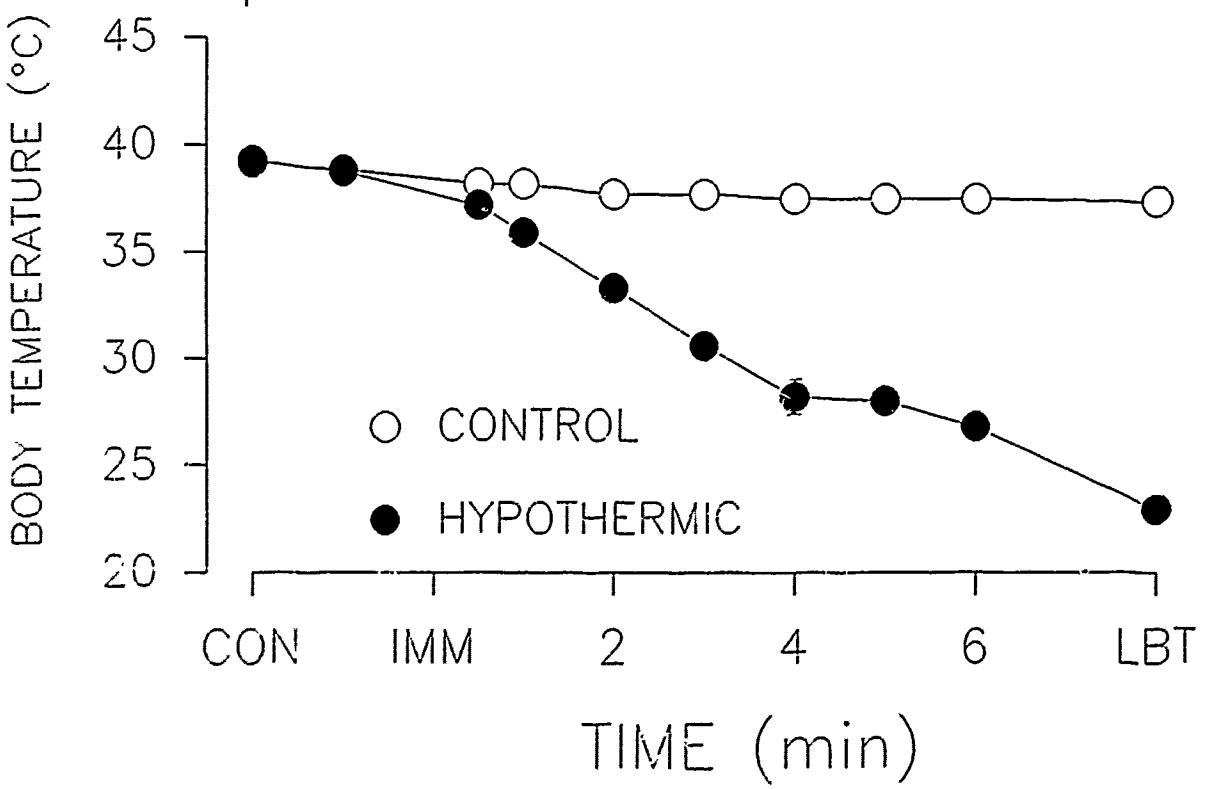
The changes we observed in the metabolic samples (FFA, glucose and lactate) are related to the elevation of NorEpi. When the energy baring metabolites can not be mobilized by NorEpi due to downregulation and the futile cycle of triglycerides within the adipose tissue does not produce the heat required then the organism can no longer thermoregulate.

NAVAL5.WP

FIGURE 1



time interval
expanded below

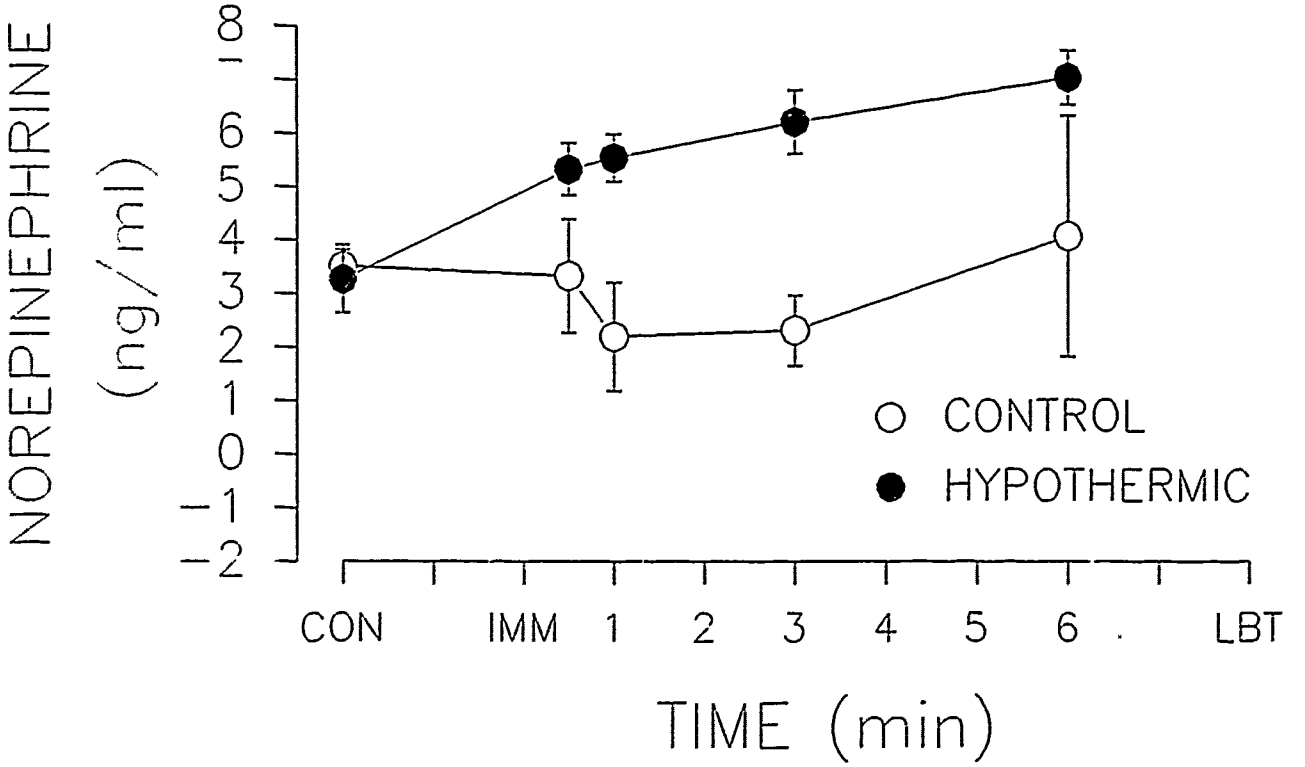


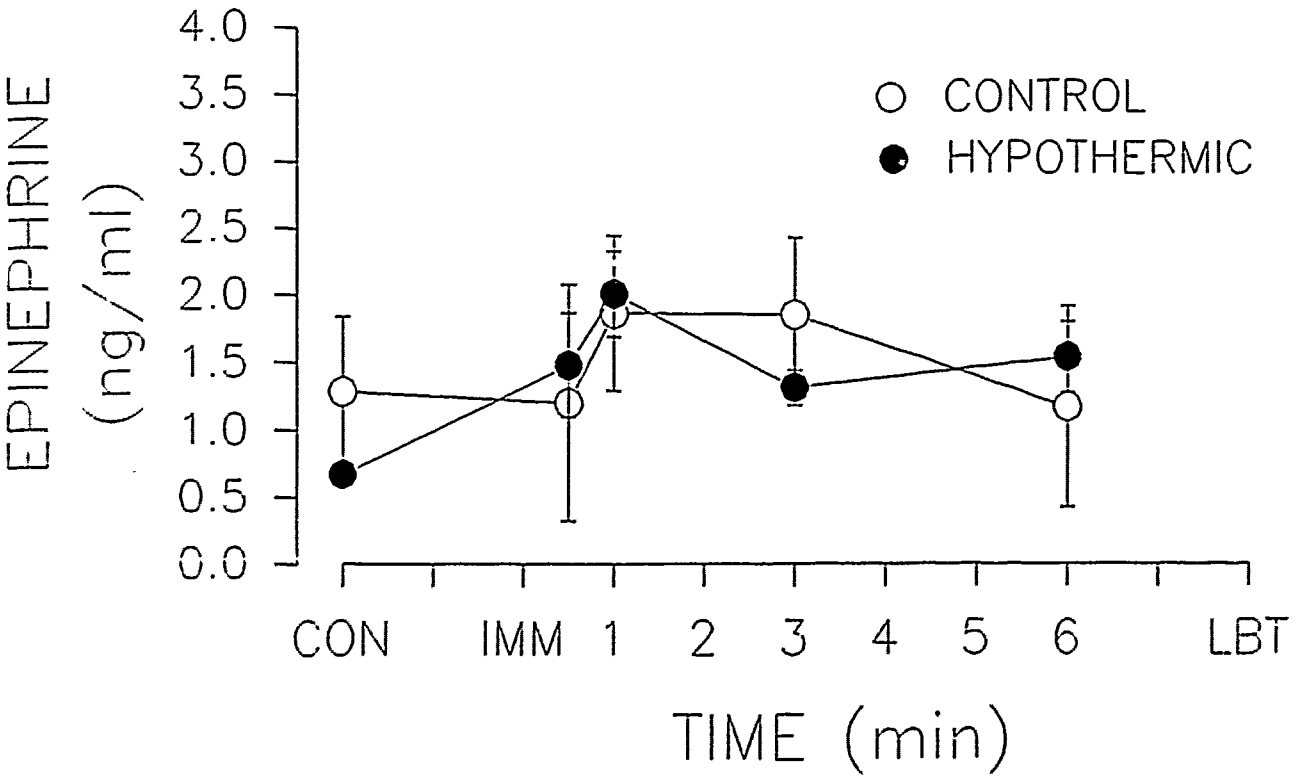
CON– CONTROL

IMM– IMMERSION

LBT– TIME OF LOWEST BODY TEMP

FIGURE 2



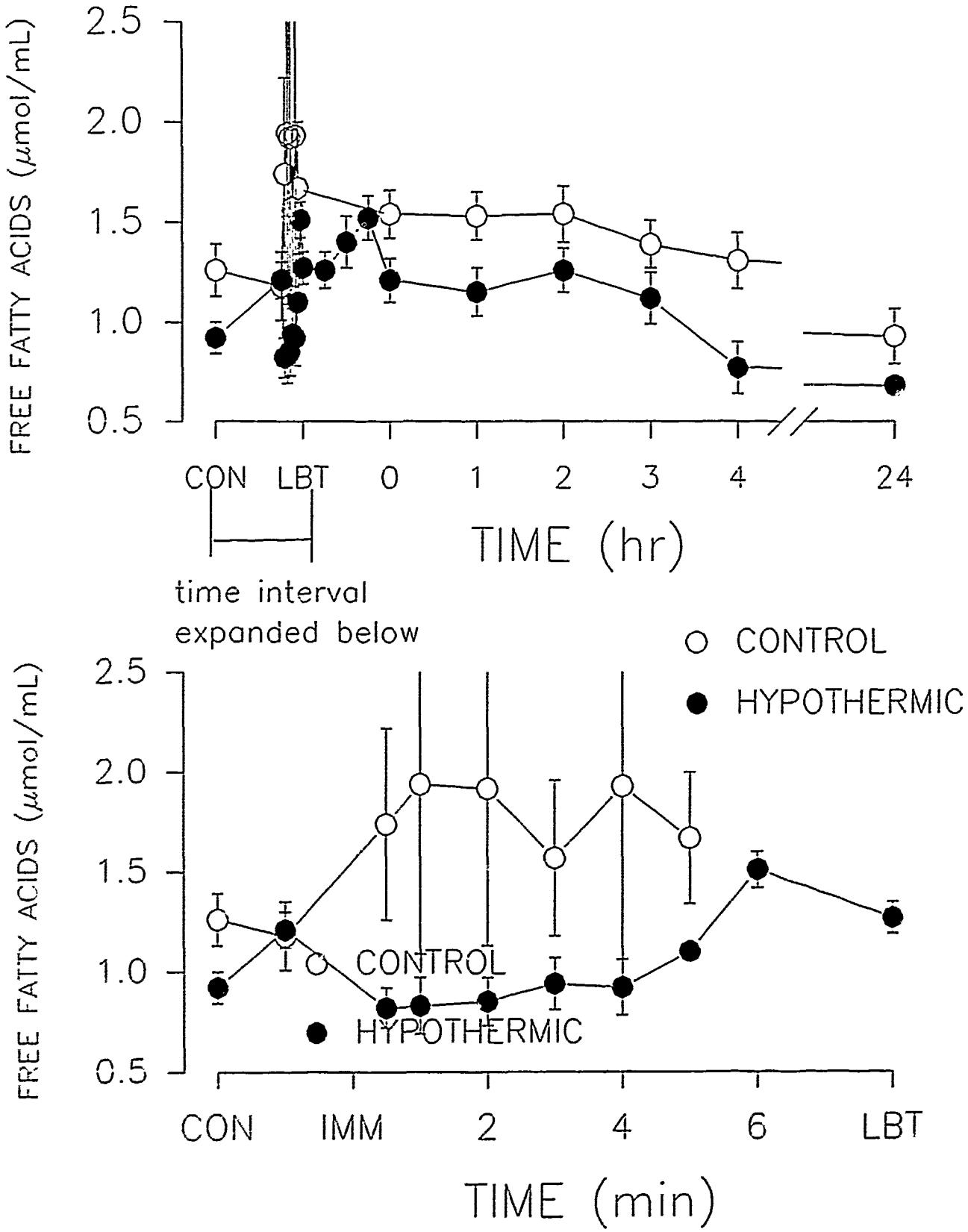


CON– CONTROL

IMM– IMMERSION

LBT– TIME OF LOWEST BODY TEMP

FIGURE 3

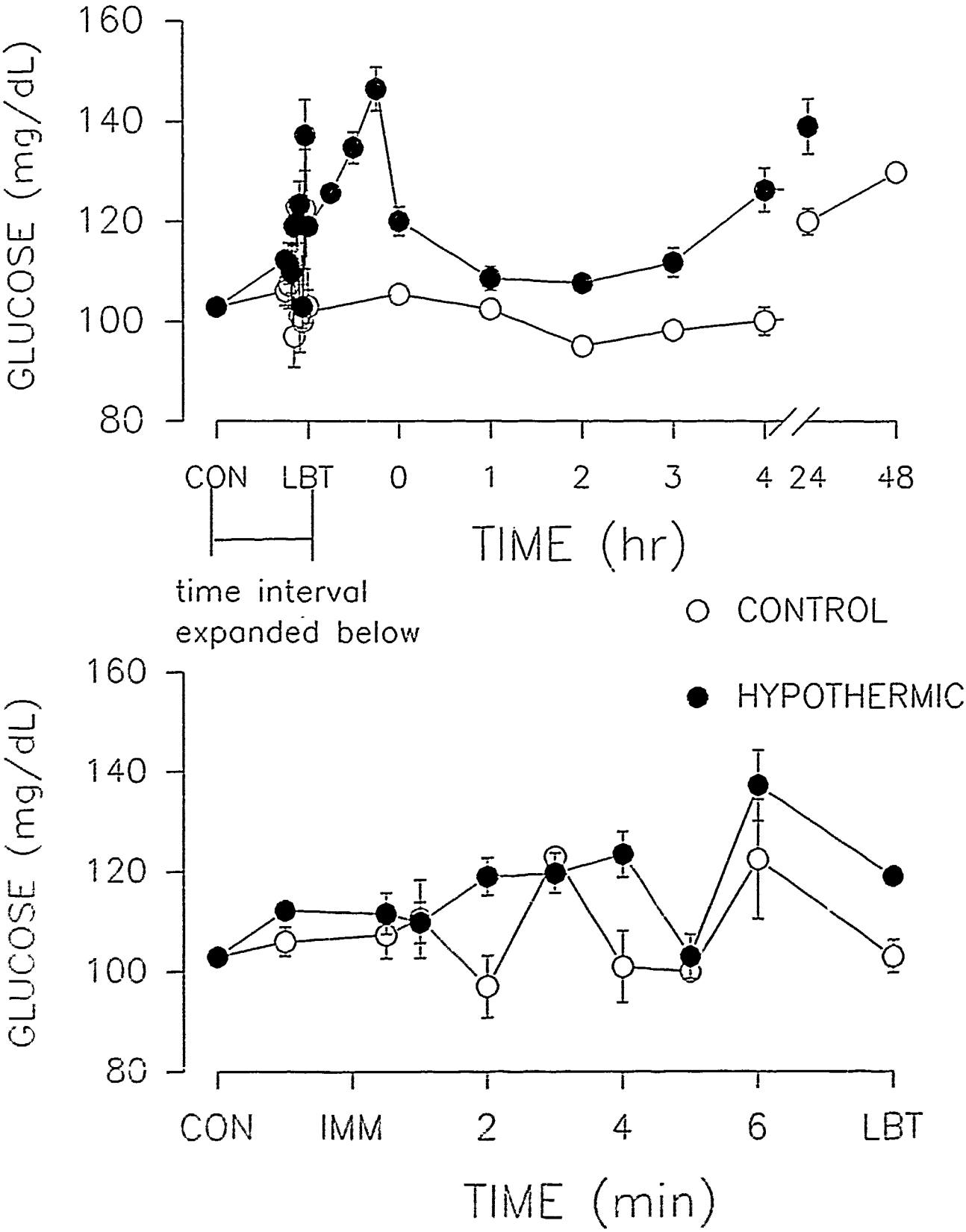


CON– CONTROL

IMM– IMMERSION

LBT– TIME OF LOWEST BODY TEMP

FIGURE 4

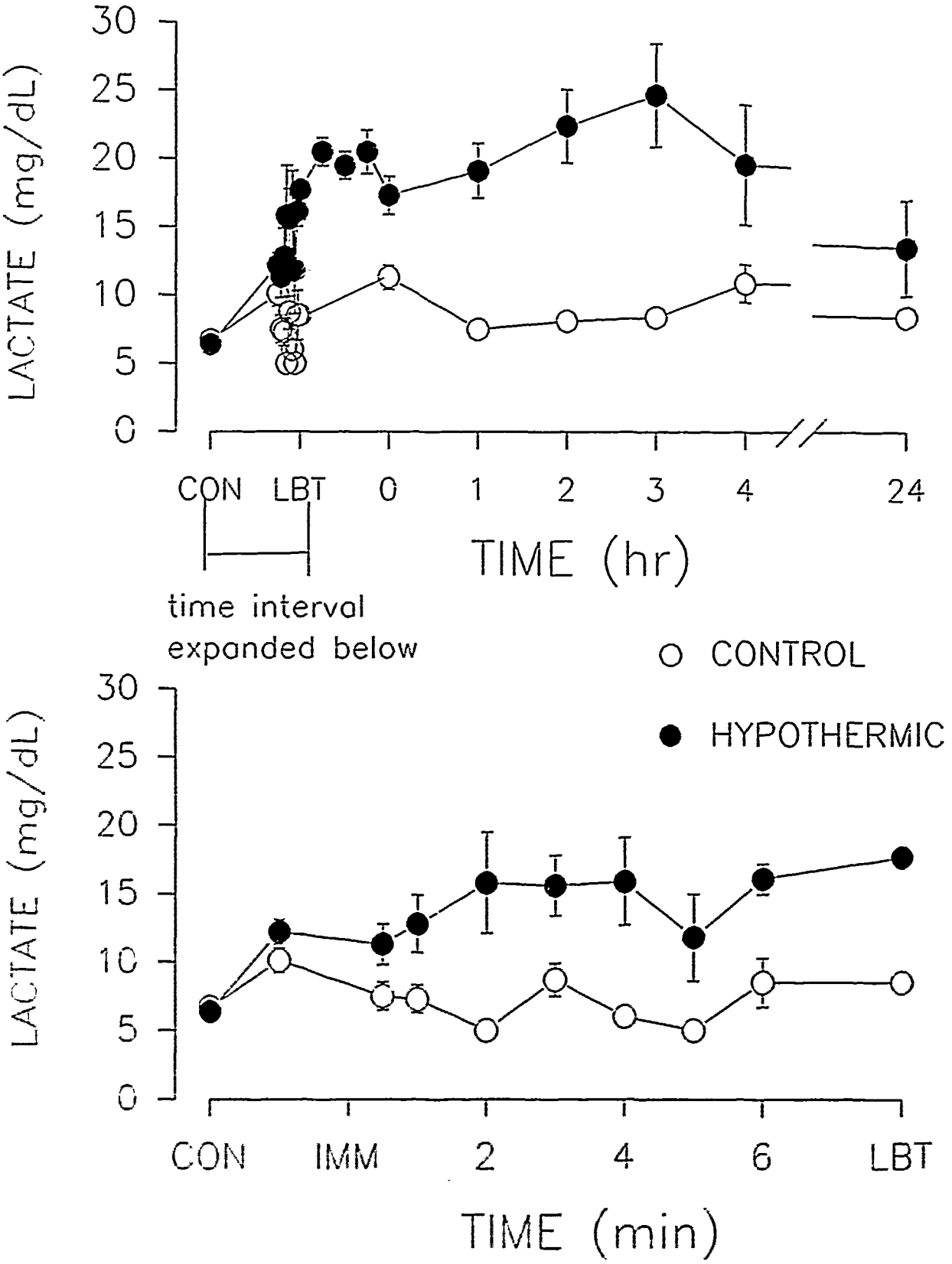


CON– CONTROL

IMM– IMMERSION

LBT– TIME OF LOWEST BODY TEMP

FIGURE 5



CON– CONTROL

IMM– IMMERSION

LBT– TIME OF LOWEST BODY TEMP

FIGURE 6

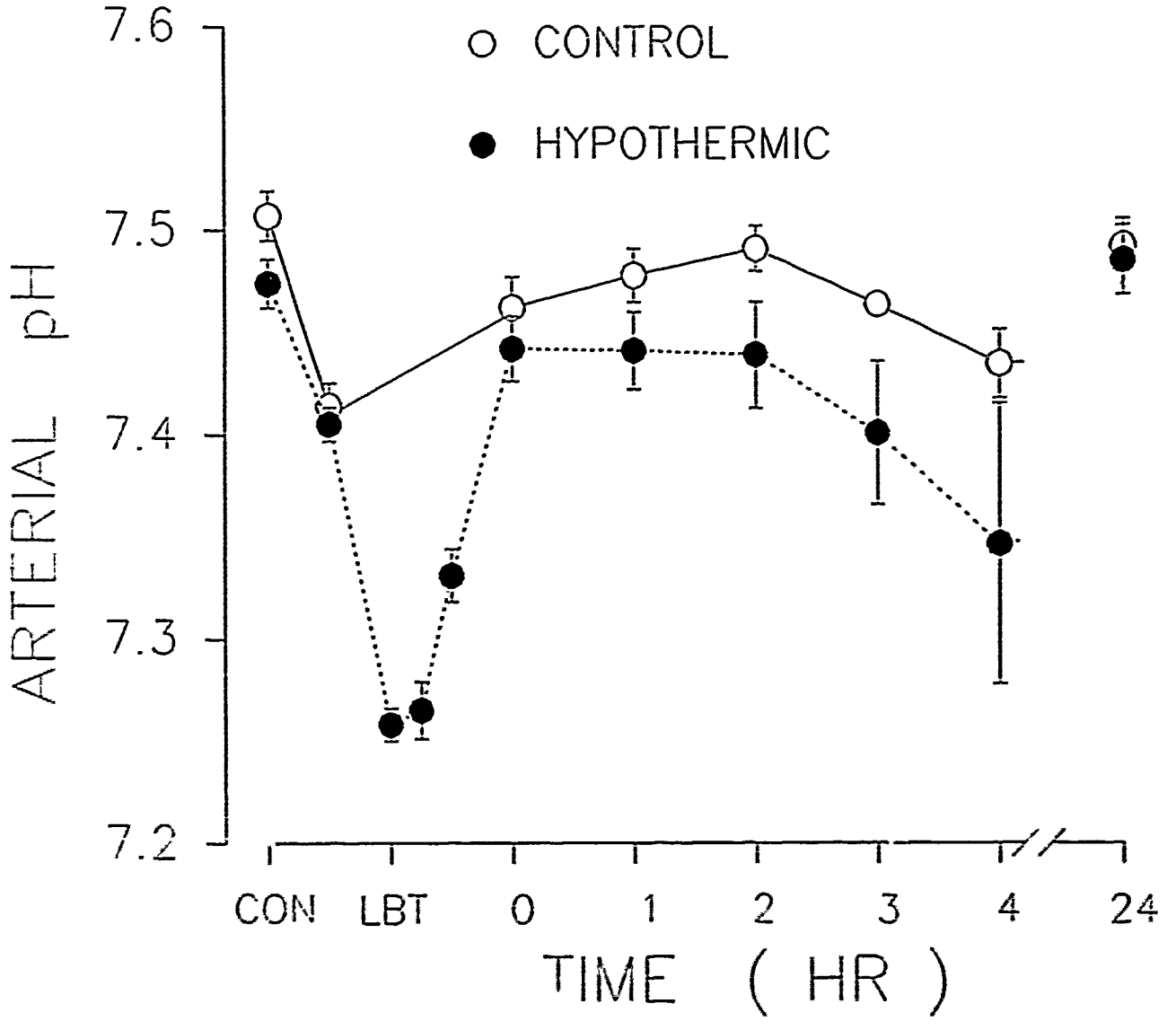
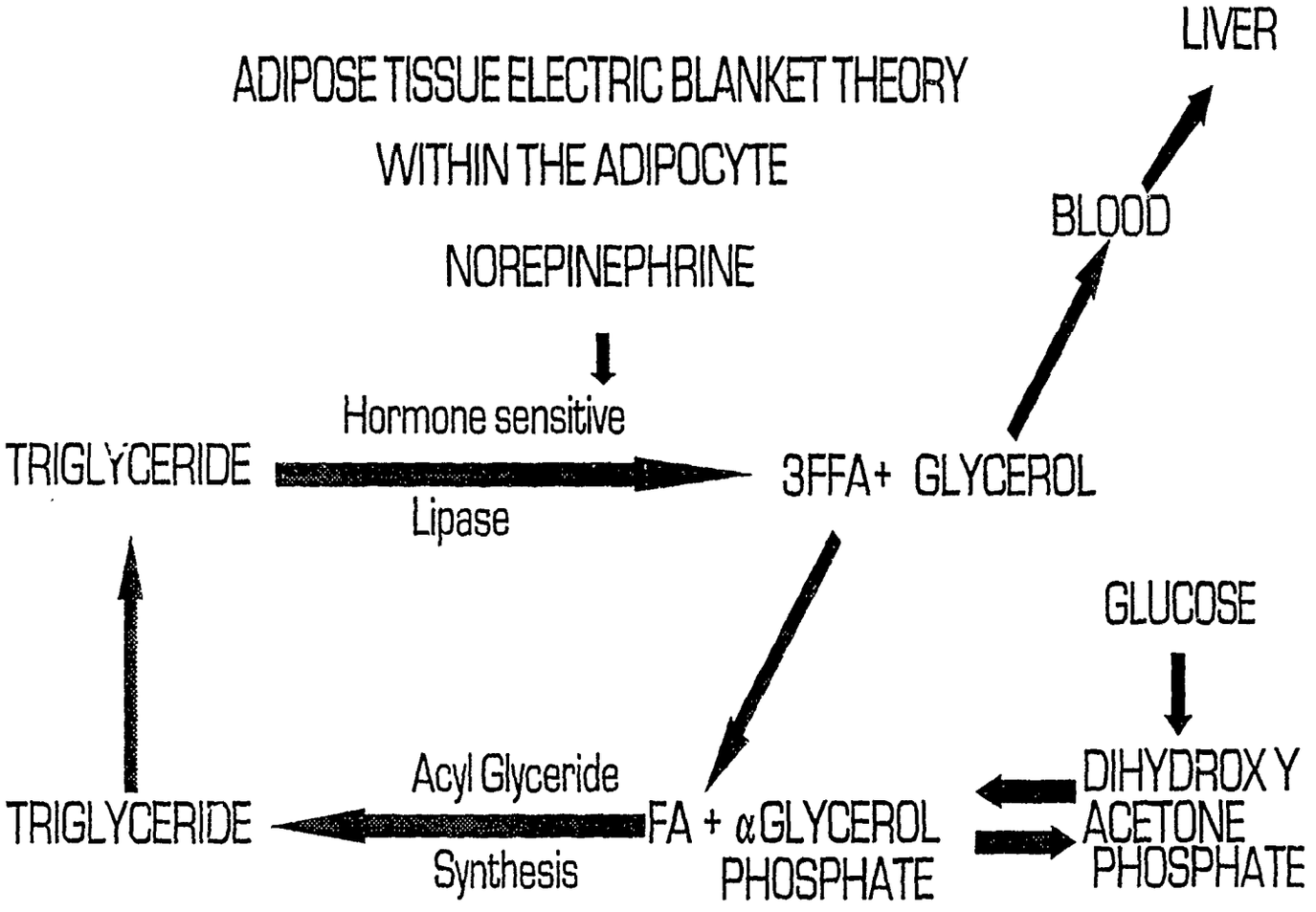

7.6
7.5
7.4
7.3
7.2
ARTERIAL pH
CONTROL
HYPOTHERMIC
CON
LBT
0
1
2
3
4
24
TIME (HR)

FIGURE 8



FUTILE CYCLE - Produces heat
much of which is preserved in the core